EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to Padina pavonica-extract in Dictyolone® and an increase in bone mineral density pursuant to Article 13(5) of Regulation (EC) No 1924/2006.

EFSA Publication

Link to article, DOI:
10.2903/j.efsa.2014.3518

Publication date:
2014

Document Version
Publisher's PDF, also known as Version of record

European Food Safety Authority

EFSA Journal 2014;12(1):3518

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to *Padina pavonica*-extract in Dictyolone® and an increase in bone mineral density pursuant to Article 13(5) of Regulation (EC) No 1924/2006[1]

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)[2, 3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from ICP Ltd, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Malta, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to *Padina pavonica*-extract in Dictyolone® and an increase in bone mineral density. The Panel considers that the *Padina pavonica*-extract in Dictyolone® is sufficiently characterised. An increase (or reduced loss) in bone mineral density is a beneficial physiological effect. The applicant presented four human intervention studies, four animal studies and two *in vitro* studies as pertinent to the health claim. No conclusions could be drawn from two of the four human studies as they were carried out with a food that did not comply with the specifications of the food which is the subject of the health claim. The two other human studies did not show an effect of the *Padina pavonica*-extract in Dictyolone® on bone mineral density. The Panel concludes that a cause and effect relationship has not been established between the consumption of *Padina pavonica*-extract in Dictyolone® and an increase (or reduced loss) in bone mineral density.

KEY WORDS

Dictyolone®, *Padina pavonica*, bone mineral density, health claims

[1] On request from the Competent Authority of Malta following an application by ICP Ltd, Question No EFSA-Q-2013-00249, adopted on 11 December 2013.

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[3] Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific opinion.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to *Padina pavonica*-extract in Dictyolone® and an increase in bone mineral density pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2014;12(1):3518, 11 pp. doi:10.2903/j.efsa.2014.3518

Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following an application from ICP Ltd, submitted for authorisation of a health claim pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of Malta, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to *Padina pavonica*-extract in Dictyolone® and an increase in bone mineral density (BMD).

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.

The food that is the subject of the health claim is a *Padina pavonica*-extract in Dictyolone®. The starting material for the extraction process is dried *Padina pavonica*, which is a brown alga commonly known as Peacock's tail. The Panel considers that the *Padina pavonica*-extract in Dictyolone® is sufficiently characterised.

The claimed effect is "improves bone density". The target population proposed by the applicant is the general population. The Panel considers that an increase (or reduced loss) in bone mineral density is a beneficial physiological effect.

The applicant presented four human intervention studies, four animal studies and two *in vitro* studies as pertinent to the health claim.

Two of the four human intervention studies were carried out with a food (i.e. lyophilised powder of *Padina pavonica*) that did not comply with the specifications of the food (i.e. *Padina pavonica*-extract in Dictyolone®) which is the subject of the health claim. The Panel considers that no conclusions can be drawn from these two studies for the scientific substantiation of a health claim on the *Padina pavonica*-extract in Dictyolone®.

In a randomised, open label, parallel human study, 40 post-menopausal women were randomised into two groups to receive daily for 12 months 200 mg *Padina pavonica*-extract in Dictyolone® plus 450 mg calcium carbonate or 450 mg calcium carbonate only. The primary outcome of the study was BMD which was measured at the screening visit and at the end of the study (i.e. at month 12) at the lumbar region and at the left hip region (femoral neck). In addition, bone turnover markers were measured at month 3 and month 6. There were no statistically significant differences for percent changes in BMD at either site (i.e. lumbar region or femoral neck) between the groups. There were no differences in bone turnover markers between the groups. The Panel notes that this study did not show an effect of the *Padina pavonica*-extract in Dictyolone® on BMD.

In another randomised, open label, parallel human study, 40 post-menopausal women were randomised into two groups to receive daily for 12 months 200 mg *Padina pavonica*-extract in Dictyolone® or 450 mg calcium carbonate. The same protocol as for the above study was followed except that BMD measurements were performed three times, i.e. at the screening (= baseline), and at month 6 and month 12. Bone turnover markers were not assessed in this study. Absolute values of BMD were transformed to percent changes of BMD prior to hypothesis testing. When using the Mann Whitney test, after 12 months the BMD was increased (as percent change from baseline) in the group which had consumed the *Padina pavonica*-extract in Dictyolone® in lumbar spine and in the femoral neck, when compared with the control group. When an analysis of variance (ANOVA) was performed on such transformed (i.e. percent changes) data, a statistically significant difference between the placebo and the *Padina pavonica*-group was found at the femoral neck only and not at the lumbar spine. When ANOVA was performed with absolute values of BMD, there were no statistically significant differences between the placebo and the *Padina pavonica* group at any time point. The repeated measures design was not taken into account in any of the provided analyses. The Panel notes the limitations of the statistical analyses performed by the applicant (i.e. transformation of data, lack

of baseline adjustments in the analysis of absolute values, lack of consideration of the repeated measures design of the study) and that the requested re-analysis of data addressing these limitations was not presented by the applicant. The Panel also notes that the results of the different statistical analyses, i.e. percent change in BMD analysed with the Mann Whitney test and ANOVA, and absolute values of BMD analysed with ANOVA, were inconsistent both between the different statistical tests and between bone sites investigated. The Panel considers that this study did not show an effect of the *Padina pavonica*-extract in Dictyolone® on BMD.

The provided animal studies did not evaluate BMD. The *in vitro* studies measured calcium accumulation in primary and cell-line osteoblasts.

In weighing the evidence, the Panel took into account that the two human studies from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of the *Padina pavonica*-extract in Dictyolone® on BMD.

The Panel concludes that a cause and effect relationship has not been established between the consumption of *Padina pavonica*-extract in Dictyolone® and an increase (or reduced loss) in BMD.

TABLE OF CONTENTS

BACKGROUND

Regulation (EC) No 1924/2006[4] harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 25/02/2013.
- The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application included a request for the protection of proprietary data.
- On 22/03/2013, during the validation process of the application, EFSA sent a request to the applicant to provide missing information.
- On 30/04/2013, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 15/05/2013.
- On 26/06/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application, and the clock was stopped on 17/07/2013, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 30/07/2013, EFSA received the requested information and the clock was restarted, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 25/09/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application, and the clock was stopped on 04/10/2013, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- On 16/10/2013, EFSA received the requested information and the clock was restarted, in compliance with Article 18(3) of Regulation (EC) No 1924/2006.
- During its meeting on 11/12/2013, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to *Padina pavonica*-extract in Dictyolone® and an increase (or reduced loss) in bone mineral density.

[4] Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: *Padina pavonica*-extract in Dictyolone® and an increase in bone mineral density.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of the *Padina pavonica*-extract in Dictyolone®, a positive assessment of its safety, nor a decision on whether the *Padina pavonica*-extract in Dictyolone® is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Institute of Cellular Pharmacology (ICP) Ltd, Unit F24/F25, MOSTA Technopark, Malta.

The application includes a request for the protection of proprietary data for three unpublished animal studies (Gutierrez et al., 2006a, b, 2011) and two *in vitro* studies (Gutierrez, 2006; Serrar et al., unpublished) in accordance with Article 21 of Regulation (EC) No 1924/2006.

Food/constituent as stated by the applicant

According to the applicant, the food that is the subject of the health claim is Dictyolone® which has as its constituent a known quantity of *Padina pavonica*-extract. *Padina pavonica* is a brown alga with a worldwide distribution.

Health relationship as claimed by the applicant

According to the applicant, *Padina pavonica* exhibits a "calcitrophic" effect, which is brought about by the synthesis and release of a substance that affects "fixation" of calcium. The applicant claimed that this would lead to an increase in bone mineral density (BMD).

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "improves bone density through calcitrophic effects and through the physiological restoration of proteinous bone, particular in bone loss brought about by the aging process on normal healthy persons".

Specific conditions of use as proposed by the applicant

The applicant has proposed a daily intake of 200 to 400 mg of *Padina pavonica*-extract, possibly in several doses, for an average body weight of about 50 to 60 kg. The target population is the general population.

ASSESSMENT

1. Characterisation of the food/constituent

The food that is the subject of the health claim is a *Padina pavonica*-extract in Dictyolone®.

The starting material for the extraction process is dried *Padina pavonica*, which is a brown alga commonly known as Peacock's tail. For the extraction, lower alkanols (e.g. ethanol) or aliphatic ketones (e.g. acetone) are used. An overview of the patented manufacturing process (EP 0 655 250 B1; US 5,961,981 B2) was provided.

Each tablet of Dictyolone® contains, on average, the extract of 500 mg of dry plant, which corresponds to 5 g of fresh plant, plus the excipients magnesium stearate, microcrystalline cellulose, silicon dioxide and talc.

The extract is standardised to its capacity to increase intracellular calcium (denominated as "calcium-fixation" by the applicant) *in vitro* in human osteoblasts (G292 cell line) following a patented procedure (FR 2 827 303; US 7,122,337 B2).

The Panel considers that the food, the *Padina pavonica*-extract in Dictyolone®, which is the subject of the health claim, is sufficiently characterised.

2. Relevance of the claimed effect to human health

The claimed effect is "increase in bone mineral density". The target population proposed by the applicant is the general population.

Contribution to the development and maintenance of normal bone throughout the lifespan is considered to be a beneficial physiological effect (EFSA NDA Panel, 2012). An increase in bone formation and/or a decrease in bone resorption are considered beneficial physiological effects when they lead to an increase (or reduced loss) in bone mineral density (BMD).

The Panel considers that an increase (or reduced loss) in bone mineral density is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The applicant performed a literature search in the company's own archive and database, where all bibliography deemed relevant by the applicant was claimed to be catalogued. Inclusion and exclusion criteria were "based on the relevance of the data presented in relation to the claim brought forward". All the documents retrieved were considered to be relevant by the applicant, since they were "related to the physiological effect of the *Padina pavonica* at cellular level related to calcium fixation".

The applicant presented four human intervention studies (Galea, 2009, PhD thesis), four animal studies (Gutierrez et al., 2005, 2006a, b, 2011; all four unpublished) and two *in vitro* studies (Serrar et al., unpublished; Gutierrez, 2006) as pertinent to the health claim.

Two of the four human intervention studies reported by Galea (2009) were carried out with a lyophilised powder (obtained before the extraction process) of *Padina pavonica* that does not comply with the specifications of the food (as described in section 1) which is the subject of the health claim. The applicant was requested to provide a rationale as to why results from studies with the lyophilised powder could be used for the substantiation of a health claim on the extract. In reply, the applicant stated that the studies which were carried out with the lyophilised powder of *Padina pavonica* were used to "help determine the effective minimal dose and help determine the interference the calcium carbonate had in the makeup of the capsule". The Panel considers that no conclusions can be drawn from the two studies carried out with a lyophilised powder of *Padina pavonica* for the scientific substantiation of a health claim on the *Padina pavonica*-extract in Dictyolone®.

In a randomised, open label, parallel human study (Galea, 2009) 40 post-menopausal women attending a bone densitometry unit in a hospital in Malta were randomised into two groups to receive daily for 12 months 200 mg *Padina pavonica*-extract in Dictyolone® plus 450 mg calcium carbonate (= 180 mg Ca) (mean age 59.3 ± 5.8 years, mean age of menopause 50.4 ± 2.6 years) or 450 mg calcium carbonate only (control group, mean age 58.0 ± 7.5 years, mean age of menopause 50.0 ± 2.9 years). Women were included if they either were postmenopausal for at least five years or were over 55 years of age, and had either osteoporosis or osteopenia as classified by a T-score of less than -1. No power calculations were provided. The primary outcome of the study was BMD which was measured by dual energy X-ray absorptiometry (DXA) at the screening visit and at the end of the study (i.e. at month 12) at the lumbar region (L2-L4) and at the left hip region (femoral neck). In addition, bone turnover markers (i.e. serum C-terminal propeptide of Type I collagen, urinary pyridinium crosslinks) were measured at month 3 and month 6. The groups were compared using the Mann Whitney test. There were no statistically significant differences for percent changes in BMD at either site (i.e. lumbar region or femoral neck) between the groups. There were no differences in bone

turnover markers between the groups. The Panel notes that this study did not show an effect of the *Padina pavonica*-extract in Dictyolone® on BMD.

In another randomised, open label, parallel human study (Galea, 2009) 40 post-menopausal women were randomised into two groups to receive daily for 12 months 200 mg *Padina pavonica*-extract in Dictyolone® (mean age 61.7 ± 5.4 years, mean age of menopause 49.1 ± 4.6 years) or 450 mg calcium carbonate (control group, mean age 60.5 ± 7.5 years, mean age of menopause 50.1 ± 2.7 years). The same protocol as for the above study was followed except that BMD measurements were performed three times, i.e. at the screening (= baseline), and at month 6 and month 12. Bone turnover markers were not assessed in this study. Two women dropped out of the study. The groups were compared using the Mann Whitney test, including results from the 38 women who completed the study. For the analysis, absolute values (in g/cm^2) of BMD were transformed to percent changes of BMD prior to hypothesis testing. After 12 months, the BMD was increased (as percent change from baseline) in the group which had consumed the *Padina pavonica*-extract in Dictyolone® in lumbar spine (mean ± SD: + 0.39 ± 2.96 %, p = 0.033) and in the femoral neck (+ 0.52 ± 3.10 %, p = 0.024) when compared with the control group (- 1.41 ± 2.58 % and - 1.81 ± 2.33 % for the BMD in lumbar spine and femoral neck, respectively). The Panel noted that the repeated measures design of the study was not taken into consideration in the analysis and that the absolute values of the data were transformed to percent changes which could have had an influence on the outcome of the analysis. Therefore, EFSA requested the applicant to provide an analysis with non-transformed (i.e. absolute) values and taking into account the design (i.e. repeated measures) of the study. EFSA also requested the applicant to provide information on the precision of the DXA measurements carried out in the study, and invited the applicant to comment on the size of the observed effect in relation to the range of error inherent in the test itself. In reply, the applicant submitted an analysis of variance (ANOVA) which compared the absolute values of BMD of the two study groups at the three time points (i.e. baseline, month 6 and month 12). There were no statistically significant differences between the placebo and the *Padina pavonica*-group at any time point. When the variables were transformed to percent changes from baseline to month 12, the ANOVA resulted in a statistically significant difference between the placebo and the *Padina pavonica*-group at the femoral neck (mean ± SD: 0.52 ± 3.10 %, p = 0.012) but not at the lumbar spine. The repeated measures design was not taken into account in the analyses. The applicant did not provide details on the precision of the DXA measurements. The Panel notes the limitations of the statistical analyses performed by the applicant (i.e. transformation of data, lack of baseline adjustments in the analysis of absolute values, lack of consideration of the repeated measures design of the study) and that the requested re-analysis of the data addressing these limitations was not presented by the applicant. The Panel also notes that the results of the different statistical analyses, i.e. percent change in BMD analysed with the Mann Whitney test and ANOVA, and absolute values of BMD analysed with ANOVA, were inconsistent both between the different statistical tests and between bone sites investigated. The Panel considers that this study did not show an effect of the *Padina pavonica*-extract in Dictyolone® on BMD.

The provided animal studies (Gutierrez et al., 2005, 2006a, b, 2011) did not evaluate BMD. The *in vitro* studies measured calcium accumulation in primary and cell-line osteoblasts (Serrar et al., unpublished) and described the patented method (FR 2 827 303; US 7,122,337 B2) referred to in section 1 (Gutierrez, 2006).

In weighing the evidence, the Panel took into account that the two human studies from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of the *Padina pavonica*-extract in Dictyolone® on BMD.

The Panel concludes that a cause and effect relationship has not been established between the consumption of *Padina pavonica*-extract in Dictyolone® and an increase (or reduced loss) in BMD.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food, *Padina pavonica*-extract in Dictyolone®, which is the subject of the health claim, is sufficiently characterised.
- The claimed effect is "improves bone density". The target population proposed by the applicant is the general population. An increase (or reduced loss) in BMD is a beneficial physiological effect.
- A cause and effect relationship has not been established between the consumption of *Padina pavonica*-extract in Dictyolone® and an increase (or reduced loss) in BMD.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on *Padina pavonica*-extract in Dictyolone® and an increase in bone mineral density pursuant to Article 13(5) of Regulation (EC) No 1924/2006 (Claim serial No: 0378_MT). February 2013. Submitted by ICP Ltd.

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Serrar M, Gutierrez G, Brincat M, Saliba C, Galea R, Salles JP and Bendhaou K (unpublished, claimed as proprietary by the applicant). The induction of calcium fixation and synthesis of extracellular matrix components by an extract from the marine alga *Padina pavonica*.

ABBREVIATIONS

ANOVA	analysis of variance
BMD	bone mineral density
DXA	dual energy X-ray absorptiometry